

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
 United States Patent and Trademark
 Office
 Box PCT
 Washington, D.C.20231
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 25 August 2000 (25.08.00)	
International application No. PCT/EP00/00690	Applicant's or agent's file reference C 2737 PCT
International filing date (day/month/year) 28 January 2000 (28.01.00)	Priority date (day/month/year) 29 January 1999 (29.01.99)
Applicant JUNGBLUT, Peter et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

26 June 2000 (26.06.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

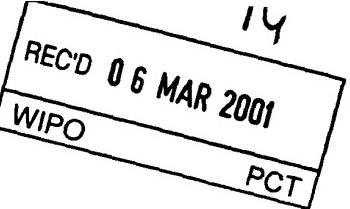
was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Olivia RANAIVOJAONA
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

100%

PATENT COOPERATION TREATY

**PCT****INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference C 2737 PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/00690	International filing date (day/month/year) 28/01/2000	Priority date (day/month/year) 29/01/1999
International Patent Classification (IPC) or national classification and IPC A61K38/16		
Applicant CHIRON BEHRING GMBH & CO. et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 0 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 26/06/2000	Date of completion of this report 01.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Ludwig, G Telephone No. +49 89 2399 8698



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/00690

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17.)*):

Description, pages:

1-69 as originally filed

Claims, No.:

1-26 as originally filed

Drawings, sheets:

1/35-35/35 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/00690

the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 5-26
 No: Claims 1-4

Inventive step (IS) Yes: Claims
 No: Claims 1-26

Industrial applicability (IA) Yes: Claims 1-26
 No: Claims

**2. Citations and explanations
see separate sheet**

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/00690

- D1: KUMAR D ET AL.: 'Identification of a 25-kilodalton protein of *Mycobacterium bovis* BCG to distinguish BCG strains from *Mycobacterium tuberculosis'* JOURNAL OF CLINICAL MICROBIOLOGY, (1996 JAN) 34 (1) 224-6 , XP002146161
- D2: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 1998 (1998-05) AMARA RAMA RAO ET AL: 'Characterization of novel immunodominant antigens of *Mycobacterium tuberculosis.'* Database accession no. PREV199800303509 XP002146135 & MICROBIOLOGY (READING), vol. 144, no. 5, May 1998 (1998-05), pages 1197-1203, ISSN: 1350-0872
- D3: URQUHART BROOKE L ET AL: "Proteomic contigs' of *Mycobacterium tuberculosis* and *Mycobacterium bovis* (BCG) using novel immobilised pH gradients.' ELECTROPHORESIS, vol. 18, no. 8, 1997, pages 1384-1392, XP000938853 ISSN: 0173-0835
- D4: BROSCH ET AL: 'USE OF A MYCOBACTERIUM TUBERCULOSIS H37RV BACTERIAL ARTIFICIAL CHROMOSOME LIBRARY FOR GENOME MAPPING, SEQUENCING, AND COMPARATIVE GENOMICS' INFECTION AND IMMUNITY,US,AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, vol. 66, May 1998 (1998-05), pages 2221-2229, XP002104659 ISSN: 0019-9567
- D5: PATENT ABSTRACTS OF JAPAN vol. 013, no. 589 (C-670), 25 December 1989 (1989-12-25) & JP 01 247094 A (AJINOMOTO CO INC;OTHERS: 01), 2 October 1989 (1989-10-02)
- D6: JUNGBLUT P R ET AL: 'Comparative proteome analysis of *Mycobacterium tuberculosis* and *Mycobacterium bovis* BCG strains: Towards functional genomics of microbial pathogens.' MOLECULAR MICROBIOLOGY, vol. 33, no. 6, 1999, pages 1103-1117, XP000938898 ISSN: 0950-382X
- P-document**

1. If the priority of the application is not valid P-document D5 could be used against

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/00690

novelty/inventive step of the application.

2. According to the application the aim of the invention is
 - 1) to provide a safe and effective vaccine for tuberculose treatment
 - 2) the development of a reliable diagnostics for tuberculosis

(cf. page 2, last two paragraphs).

- 3. Having regard to item 1) as stated above (provision of a vaccine for tuberculose treatment) it appears that the application represents basic research whose practical application is only of hypothetical nature given that any evidence for such an application is lacking.
 - 3.1 The application does not contain any examples which support the practical applicability of this claimed subject-matter.
 - 3.2 What has been found by the applicant by 2D-analysis appear to be intracellular proteins which are differentially expressed in a virulent Mycobacterium strain (M. tuberculosis) as compared to a non-virulent M. strain (M.bovis).

At present evidence there is no apparent evidence that the respective medical problem is solved by the application i.e. that these proteins can be used for the purpose of providing a vaccine for tuberculose treatment.
- 4. In view of the above an inventive step appears to be lacking in the claims 1-26, having regard of the problem of providing a safe and effective vaccine for tuberculose treatment as identified above under item 1).

- 5. Having regard to item 2) as stated above (development of a reliable diagnostics for tuberculosis) the problem is known in the art and has been addressed by documents D1-D5:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/00690

To differentiate between *M. bovis* BCG reactivation and *M. tuberculosis* infection a 25 kDa protein was identified in document D1 which is unique for BCG strains but not for *M. tuberculosis*.

For immunodiagnosis of tuberculosis in document D2 a protein was identified in tuberculosis patients' serum which was not found in BCG-vaccinated individuals.

For the same purpose as in documents D1-D2 differences in protein expression were observed by 2D-analysis of *M. tuberculosis* and *M. bovis* BCG in document D3.

In document D4 a chromosome library of *M. tuberculosis* was made for the same purpose.

Document D5 reports on the expression of the MPB64/(MPT64) protein which is expressed in *M. tuberculosis* but not in *M. bovis* BCG (cf. the application on page 41, last paragraph and page 66, second protein from the top).

- 5.1 Claims 1-4 (claims 1-3) are not regarded as novel vis-a-vis documents D1 or D2 (document D5).

Claims 5 and 7-26 are not regarded as inventive in view of these documents.

- 5.2 Claims 1-5 and 7-26 are not regarded as inventive in view of document D5.
- 5.3 The specific proteins indicated in claim 6 appear not to have been identified before as being specific for *M. tuberculosis* as compared to *M. bovis* BCG (cf. page 40, paragraph 2).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference: C 2737 PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/00690	International filing date (day/month/year) 28/01/2000	(Earliest) Priority Date (day/month/year) 29/01/1999
Applicant CHIRON BEHRING GMBH & CO. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of Invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

IDENTIFICATION OF SPECIFIC DIFFERENTIALLY EXPRESSED MYCOBACTERIAL ANTIGENS

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/00690

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	A61K38/16	A61K39/04	C07K19/00	C12N15/31	C12N15/62
	A61K31/7088	C07K16/12	A61K39/40	G01N33/569	A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, BIOSIS, WPI Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; May 1998 (1998-05) AMARA RAMA RAO ET AL: "Characterization of novel immunodominant antigens of <i>Mycobacterium tuberculosis</i>." Database accession no. PREV199800303509 XP002146135 abstract & MICROBIOLOGY (READING), vol. 144, no. 5, May 1998 (1998-05), pages 1197-1203, ISSN: 1350-0872</p> <p>---</p> <p style="text-align: right;">-/--</p>	1-3, 6-8, 14-17, 20

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

30 August 2000

Date of mailing of the international search report

13/09/2000

Name and mailing address of the ISA

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 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Covone, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/00690

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	URQUHART BROOKE L ET AL: "'Proteomic contigs' of <i>Mycobacterium tuberculosis</i> and <i>Mycobacterium bovis</i> (BCG) using novel immobilised pH gradients." ELECTROPHORESIS, vol. 18, no. 8, 1997, pages 1384-1392, XP000938853 ISSN: 0173-0835 abstract page 1385, right-hand column, paragraph 1 page 1391, left-hand column, paragraph 1 ---	1-8, 16, 17
X	KUMAR D ET AL.: "Identification of a 25-kilodalton protein of <i>Mycobacterium bovis</i> BCG to distinguish BCG strains from <i>Mycobacterium tuberculosis</i> " JOURNAL OF CLINICAL MICROBIOLOGY, (1996 JAN) 34 (1) 224-6 , XP002146161 the whole document ---	1-8, 14-17, 20
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 589 (C-670), 25 December 1989 (1989-12-25) & JP 01 247094 A (AJINOMOTO CO INC; OTHERS: 01), 2 October 1989 (1989-10-02) abstract ---	1-3, 6-8, 14-17, 20
A	BROSCH ET AL: "USE OF A MYCOBACTERIUM TUBERCULOSIS H37RV BACTERIAL ARTIFICIAL CHROMOSOME LIBRARY FOR GENOME MAPPING, SEQUENCING, AND COMPARATIVE GENOMICS" INFECTION AND IMMUNITY, US, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, vol. 66, May 1998 (1998-05), pages 2221-2229, XP002104659 ISSN: 0019-9567 abstract page 2228, right-hand column, paragraph 2 ---	1-26
A	FR 2 752 425 A (PASTEUR INSTITUT) 20 February 1998 (1998-02-20) page 5, line 22 -page 6, line 6 claims ---	1-26
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/00690

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	JUNGBLUT P R ET AL: "Comparative proteome analysis of <i>Mycobacterium tuberculosis</i> and <i>Mycobacterium bovis</i> BCG strains: Towards functional genomics of microbial pathogens." MOLECULAR MICROBIOLOGY, vol. 33, no. 6, 1999, pages 1103-1117, XP000938898 ISSN: 0950-382X abstract page 1114, right-hand column, paragraph 3 page 1115, left-hand column, paragraphs 1,2 -----	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/00690

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
JP 01247094 A	02-10-1989	JP	2624759 B	25-06-1997
FR 2752425 A	20-02-1998	AU	4018397 A	06-03-1998
		EP	0918854 A	02-06-1999
		WO	9807847 A	26-02-1998